

Appl. No. 10/091,300  
Amtd. dated Jun. 22, 2004  
Reply to Office Action dated Dec. 25, 2003

Docket No. 11245/46211

### III. REMARKS/ARGUMENTS

Various amendments have been made to the specification and claims. Paragraphs 1, 91, and 168, have been amended. These amendments update the specification to include the issued patent numbers in response to the Office's objection. Claims 1, 11, 23, and 62 have been amended and Claims 6, 10, 18, 22, 63, and 65 have been withdrawn. These claims have been amended and/or withdrawn in response to the Office's objection as drawn to a non-elected invention. Claims 25 and 26 have also been amended. These amendments were made to change their dependency. Applicants submit that the amendments to the specification and claims are fully supported by the specification, and no new matter is added.

In the Office Action, various objections and rejections were set forth as follows: (a) the specification was objected to based on the recitation of application numbers that have since issued as patents; (b) Claims 1 and 62 are objected to because they are broadly drawn to a non-elected invention; (c) Claims 1-14, 16-26, 28, 62-63, 65, and 67 are rejected under 35 U.S.C. § 103(a) as obvious over Rockwell (U.S. Patent No. 6,448,077) in view of Petit et al. (Am. J. Pathol., 151(6): 1523-30 (1997)), as evidenced by Kawamoto et al.; (d) Claims 1-5, 7-14, 16-17, 19-26, 28, 62-63, 65, and 67 are rejected under 35 U.S.C. § 103(a) as obvious over Rockwell et al. (Mol. Cell. Diff., 3(4): 315-335 (1995)) in view of Queen et al. (U.S. Patent No. 5,530,101) and Fan et al. (Cancer Res., 53: 4637-42 (1993)) and Siemeister et al. (Cancer and Metastasis Reviews, 17: 241-248 (1998)); and (e) Claims 1, 5, 7-8, 10-14, 17, 19-26, 28, 62-63, 65, and 67 are provisionally rejected under the judicial doctrine of obviousness-type double patenting over Claims 1, 2, 15, 16, 25-26, and 42 of co-pending U.S. Application No. 09/798,689 in view of Queen et al.

Appl. No. 10/091,300  
Amtd. dated Jun. 22, 2004  
Reply to Office Action dated Dec. 25, 2003

Docket No. 11245/46211

**A. Objection to the Specification**

The Office objected to the specification based on the recitation of application numbers that have since issued as patents. In response, Applicants have updated the specification to include the issued patent numbers and request withdrawal of the objection.

**B. Objection to Claims 1 and 62**

The Office objected to Claims 1 and 62 because they are broadly drawn to a non-elected invention. In response, Applicants have amended Claims 1 and 62 to recite only the elected invention and request withdrawal of the objection.

**C. Obviousness Rejection of Claims 1-14, 16-26, 28, 62-63, 65, and 67**

The Office rejected Claims 1-14, 16-26, 28, 62-63, 65, and 67 as obvious according to § 103(a) over Rockwell (U.S. Patent No. 6,448,077) in view of Petit et al. (Am. J. Pathol., 151(6): 1523-30 (1997)), as evidenced by Kawamoto et al. Applicants respectfully disagree and request withdrawal of the present rejection.

The Office asked Applicants to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made. Applicants submit that the claims recited in the present application, as well as the claims in all related applications, are commonly owned by the assignee, ImClone Systems Incorporated.

The present invention claims a method to reduce or inhibit tumor growth in a mammal by utilizing a VEGF receptor (VEGFR) antagonist combined with an EGFR antagonist, wherein the VEGFR and EGFR antagonists are antibodies. None of the cited references teach or suggest that a VEGFR antibody should be combined with an EGFR antibody in order to enhance its affects against tumor proliferation. The two antibodies tackle tumor proliferation by different

Appl. No. 10/091,300  
Amdt. dated Jun. 22, 2004  
Reply to Office Action dated Dec. 25, 2003

Docket No. 11245/46211

mechanisms and one of ordinary skill in the art would not be motivated to combine such different treatment mechanisms with any reasonable expectation of success.

As discussed by the Office, Rockwell discloses the role of activated VEGFR in tumor proliferation and teaches neutralizing VEGFR using an anti VEGFR antibody that blocks ligand, and specifically, chimeric and humanized monoclonal antibodies that bind to an extracellular domain of VEGFR. However, the role of EGFR in tumor proliferation is not disclosed in this patent and, as the Office concedes, anti-EGFR antibodies are specifically not taught. In addition, the Office describes that Petit teaches inhibiting tumor growth with a chimeric anti-EGFR antibody (C225), which resulted in inhibition of VEGF expression, both at the mRNA and protein levels.

The Office has not set a *prima facia* case of obviousness. See MPEP § 2114.06. Although the Office alleges that it is *prima facia* obvious to combine two components that are taught by the prior art to be useful for the same purpose, Applicants submit that anti-VEGFR antibodies and anti-EGFR antibodies are not recognized by those skilled in the art as equivalents.

In fact, the two components are not even functionally or structurally equivalent. An anti-VEGFR antibody, according to the present invention, binds VEGFR, thereby inactivating the intrinsic kinase activity of VEGFR to transduce a signal. Although the present invention is not limited by any particular mechanism of VEGF receptor neutralization, anti-VEGFR antibodies bind to VEGFR and prevent binding of the VEGF ligand to the extracellular binding domain of the VEGFR. In contrast, an anti-EGFR antibody, according to the present invention, binds to EGFR and inhibits EGFR activation, thereby inhibiting the tyrosine kinase activity of EGFR, and preventing receptor autophosphorylation and the phosphorylation of other proteins involved in the various EGFR signaling pathways. Clearly these two antibodies bind to and inhibit two different receptors and cannot be considered functionally or structurally equivalent.

Appl No. 10/091,300  
Amdt. dated Jun. 22, 2004  
Reply to Office Action dated Dec. 25, 2003

Docket No. 11245/46211

Although Petit teaches that an anti-EGFR antibody functions to inhibit expression of the ligand VEGF, specifically the expression of mRNA encoding VEGF and expression of the VEGF protein, this does not lead to the conclusion that the art recognizes anti-EGFR antibodies and anti-VEGFR antibodies as equivalents. For the two to be considered equivalents, there must be some teaching or suggestion in the art that an anti-EGFR antibody will bind with VEGFR and prevent its ligands from binding the receptor *and* the anti-VEGFR antibody will bind EGFR and prevent its ligands from binding the receptor, according to the present description of an anti-VEGFR antibody. The Office has not provided any such teaching or suggestion in the references cited.

Thus, neither Rockwell nor Petit teach or suggest Applicants' invention. For the above reasons, Applicants submit that there is no teaching or suggestion in the references cited that the different treatment plans could be combined without losing their selectivity and activity against tumor cells, while their effect on normal cells is unknown. Likewise, one of ordinary skill in the art would not consider combining the VEGFR antibody along with an EGFR antibody in a kit, based on the teachings or suggestions in the cited references.

**D.      Obviousness Rejection of Claims 1-5, 7-14, 16-17, 19-26, 28, 62-63, 65, and 67**

The Office rejected Claims 1-5, 7-14, 16-17, 19-26, 28, 62-63, 65, and 67 as obvious under § 103(a) over Rockwell et al. (Mol. Cell. Diff., 3(4): 315-335 (1995)) in view of Queen et al. (U.S. Patent No. 5,530,101) and Fan et al. (Cancer Res., 53: 4637-42 (1993)) and Siemeister et al. (Cancer and Metastasis Reviews, 17: 241-248 (1998)). Applicants respectfully disagree and request withdrawal of the present rejection.

Applicants submit that the Office has not set forth a *prima facia* case of obviousness. To establish *prima facia* obviousness, the prior art references, when combined, must teach or suggest all the claim limitations, there must be some suggestion or motivation to combine the reference teachings and a reasonable expectation of success. M.P.E.P. § 2143. The Office

Appl. No. 10/091,300  
Amdt. dated Jun. 22, 2004  
Reply to Office Action dated Dec. 25, 2003

Docket No. 11245/46211

asserts with each rejection that it was *prima facia* obvious to combine antibodies that bind VEGFR and EGFR. However, as discussed below, there is simply no art cited that supports this assertion.

Although not explicitly stated, it appears that the Office is alleging that Rockwell (1995) teaches combination therapy using an anti-EGFR antibody and an anti-VEGFR antibody. This is simply not the case. According to the Office, Rockwell (1995) teaches neutralizing antibodies to EGFR and VEGFR for use in treatment of tumors. The Office then cites a passage in Rockwell (1995) discussing the efficacy of combination therapies. A review of the complete citation makes it clear that the combination therapies referred to are a combination of a single antibody with a chemotherapeutic agent:

Furthermore, there is mounting preclinical and clinical data that combination therapies may be more efficacious than single agent use. This notion is supported by the experimental data described for the anti-EGFR monoclonal antibody C225. . . . The possibility exists that the generation of neutralizing antibodies to many of these [protein tyrosine kinase] receptors will also find utility as anti-cancer agents alone or *in combination with chemotherapeutics*.

Rockwell (1995) at p. 327-28 (emphasis added). The experimental data described for C225 is in combination with chemotherapeutics such as cisplatin and doxorubicin. There is absolutely no teaching or suggestion in Rockwell (1995) to combine an anti-VEGFR antibody with an anti-EGFR antibody according to the presently claimed invention.

None of the remaining references cited by the Office provide any teaching or suggestion to combine an anti-VEGFR antibody with an anti-EGFR antibody. As discussed by the Office, Queen simply teaches chimeric and humanized antibodies; Fan merely teaches anti-EGFR antibodies and their use in combination with a chemotherapeutic agent; and Siemester only teaches that VEGFR are upregulated during angiogenesis, e.g., during tumor growth, and that an anti-EGFR neutralizing antibody decreased expression of the ligand VEGF.

Appl. No. 10/091,300  
Amtd. dated Jun. 22, 2004  
Reply to Office Action dated Dec. 25, 2003

Docket No. 11245/46211

**E. Double-Patenting Rejection of Claims 1, 5, 7-8, 10-14, 17, 19-26, 28, 62-63, 65, and 67**

The Office provisionally rejected Claims 1, 5, 7-8, 10-14, 17, 19-26, 28, 62-63, 65, and 67 under the judicial doctrine of obviousness-type double patenting over Claims 1, 2, 15, 16, 25-26, and 42 of co-pending U.S. Application No. 09/798,689 in view of Queen et al. Applicants respectfully disagree with this rejection. However, in the interest of advancing prosecution, Applicants will submit a terminal disclaimer upon issuance of the '689 application, which was recently allowed.

Appl. No. 10/091,300  
Amndt. dated Jun. 22, 2004  
Reply to Office Action dated Dec. 25, 2003

Docket No. 11245/46211

**IV. CONCLUSION**

Applicants believe that the present application is in condition for allowance, and respectfully request that a timely Notice of Allowance be issued in this case. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

The Office is authorized to charge any fees that may be necessary for consideration of this paper to Kenyon & Kenyon Deposit Account No. 11-0600.

Respectfully submitted,

KENYON & KENYON

  
\_\_\_\_\_  
Kathryn M. Limb  
Reg. No. 46,885  
One Broadway  
New York, NY 10004  
(212) 908-6277 (telephone)  
(212) 425-5288 (facsimile)

Dated: June 22, 2004